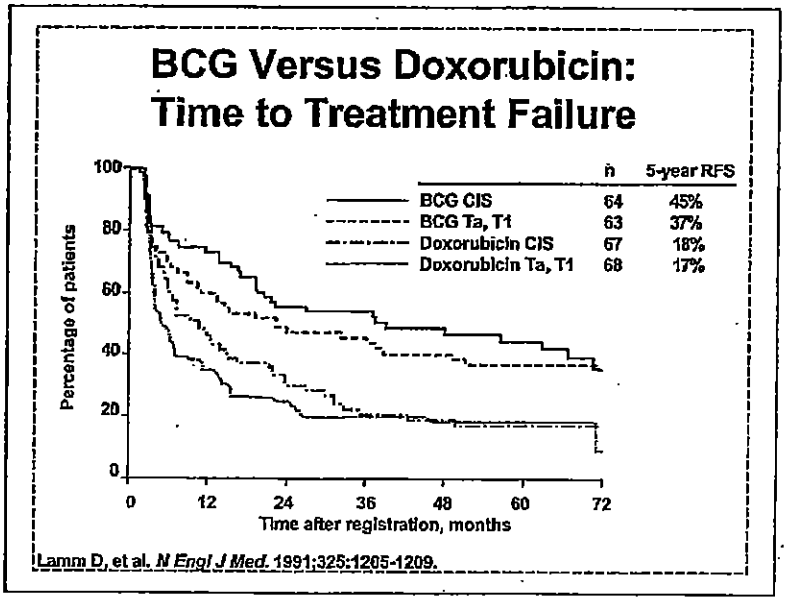
Intravesical BCG: More Effective Than Chemotherapy for Reducing Rate of Recurrence and Progression

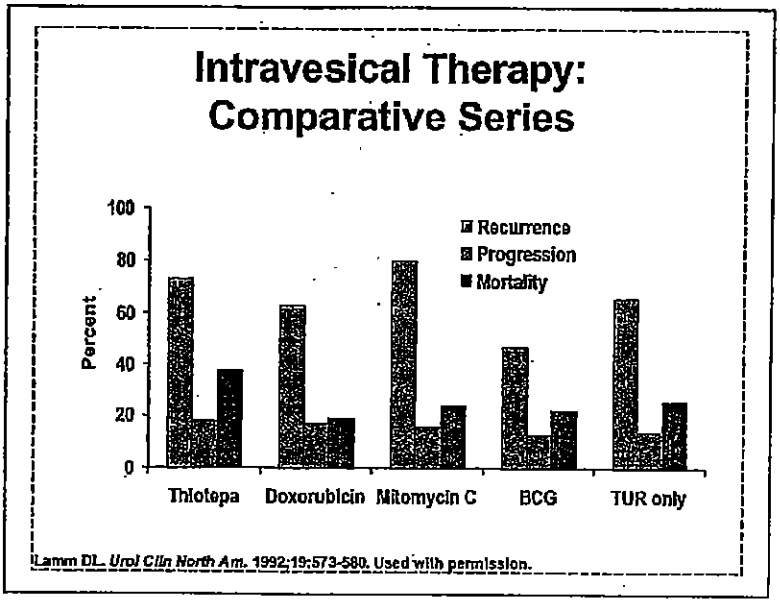
		Recurrence Rate, %			Progression Rate, %			
Agent	No. Patients	Ctrl	Rx	Net Benefit	Ctrl	Rx	Net Benefit	*P* Value
Chemotherapy	3,405	51	38	13	7	6	1	NS
BCG	496	72	32	40	23	13	10	.03

BCG = Bacillus Calmette-Gu rin.
Adapted from Lamm DL. *Eur Urol.* 1995;27(suppl 1):2-8.

Intravesical immunotherapy with bacillus Calmette-Gu rin (BCG) has been shown to be substantially more effective than intravesical chemotherapy in reducing the rate of recurrence and progression. In a retrospective review of 3,405 patients treated with chemotherapy versus 496 patients treated with BCG, intravesical BCG produced a 40% decrease in the rate of recurrence and a 10% decrease in the rate of progression ($P = .003$).[13] In contrast, intravesical chemotherapy produced only a 13% decrease in the rate of recurrence and no benefit in terms of the rate of progression.



In this trial reported by Lamm et al,[14] time to treatment failure (TTF) was also dramatically improved among patients treated with BCG compared with doxorubicin. The greater benefit of BCG was evident among patients with both papillary tumors (37% versus 17% 5-year relapse-free survival; $P = .015$) and CIS (45% versus 18% 5-year relapse-free survival). Among patients with Ta or T1 papillary tumors, the median TTF was 23 months with BCG versus 10 months with doxorubicin. Among patients with CIS, the median TTF was 39 months for BCG versus only 5 months for doxorubicin. Further, BCG produced a complete response in 70% of patients, compared with 34% for the doxorubicin-treated patients ($P<.001$).



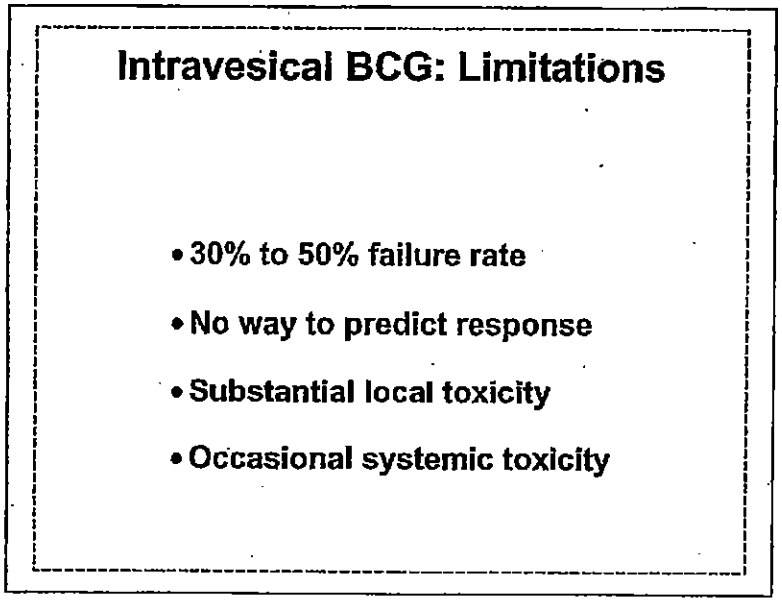
In a comparative series of intravesical therapies, BCG clearly reduced the rate of recurrence compared with chemotherapy or TUR alone[15]; however, the rate of progression and mortality was not substantially altered by any of these intravesical therapies compared with surgery alone. It appears, therefore, that intravesical immunotherapy with BCG may reduce the rate of progression, but may not ultimately prevent progression or improve survival compared with surgery alone.

Intravesical BCG: Lessons From Long-Term Experience

- Single 6-week course not enough
- Delays but does not prevent progression
- Early recurrences are ominous
- New strategies needed
  - More intensive induction regimen
  - Maintenance therapy
  - BCG enhancers

We have learned several lessons from long-term experience with intravesical BCG therapy: A single 6-week course of therapy is not sufficient; BCG appears to delay progression more effectively than chemotherapy, but does not appear to effectively prevent progression; and patients who recur early following BCG therapy generally have a poor prognosis. Adjuvant immunotherapy for superficial bladder cancer is clearly not optimal. New strategies might include more intensive induction regimens, effective maintenance therapy, and strategies to enhance the activity of BCG therapy.

add Corvette data (AUA). Abstract Superficial
Long-term BCG. – 70% disease free
(some of these PB. got maintenance tx.)



In addition, BCG has a number of other limitations. These include a 30% to 50% failure rate (at which point patients are typically refractory to re-treatment with BCG), the inability to predict who is most likely to respond to BCG, and the substantial local and systemic toxicity of intravesical BCG. All of these limitations suggest that we need to continue to search for new therapeutic strategies.

Intravesical BCG: Toxicity

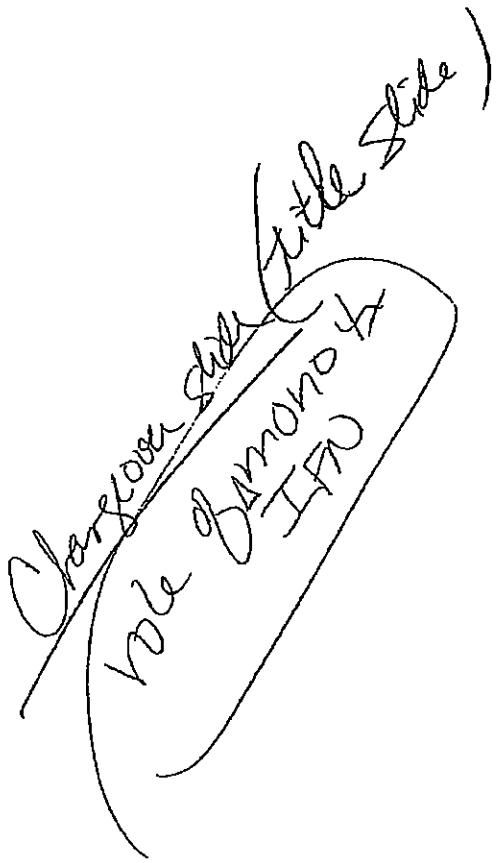
Minor		Major	
• Cystitis	91%	• Temperature >39.5¡C	3%
• Hematuria	43%	• Granulomatous prostatitis	1%
• Fever, low grade	29%	• Major hematuria	1%
• Malaise	24%	• Hepatitis/ pneumonitis	0.7%
• Nausea	5%	• Arthritis	0.5%
		• Epididymitis-orchitis	0.4%
		• Sepsis	0.4%
		• Ureteral obstruction	0.3%
		• Contracted bladder	0.2%

The major and minor toxicities associated with intravesical BCG therapy are listed here. Cystitis, hematuria, and mild flu-like symptoms are the most common adverse events associated with instillation of BCG into the bladder. Other more serious adverse events, including high, uncontrollable fever, granulomatous prostatitis, and major hematuria, may be dose limiting. For these reasons, many patients are unable to tolerate BCG therapy. Furthermore, some patients are not candidates for BCG therapy because of immunosuppression.

See section in monograph from [redacted] ... Lenny's

Table w/ tox.

add: Dr. Gonelas slide



Intravesical Interferon alfa-2b: Eradication of Residual Disease

Study	Tumor type	IFN-α2b dose	Response no. (%)	Duration, months
Oliver, 1986	pTCC	50 MU*	3/8 (37.5) CR 3/8 (37.5) PR	ND
	CIS		0	
Torti, 1988	pTCC	50 - 1,000 MIU	4/16 (25) CR	17.5+ (mean)
	CIS	50 - 1,000 MIU	6/19 (32) CR	21+ (mean)
Glashan, 1990	CIS	10 MIU	2/38 (5) CR	18
	CIS	100 MIU	20/47 (43) CR 11/47 (23) PR	12+ (median)

*Lymphoblastoid interferon.

Oliver RTD, et al. *Br J Cancer*. 1986;53:432. Abstract. Torti F, et al. *J Clin Oncol*. 1988;6:476-483. Glashan R, et al. *J Urol*. 1990;144:858-861.

Intravesical immunotherapy with the alpha interferons (IFN-α) has also been investigated. Several trials listed here have investigated intravesical interferon alfa-2b (IFN-α2b) in patients with residual papillary tumors (pTCC) or carcinoma in situ (CIS).[16-20] Response rates ranging from 25% to 75% have been reported in patients with residual pTCC treated with ≥50 million International Units (MIU) of IFN-α2b. Response rates up to 66% have been reported in patients with CIS. In CIS patients treated with 100 MIU IFN-α2b, Glashan et al[18] observed a 43% complete response (CR) rate, with a median duration of CR >12 months. These studies suggested that a dose of 50 to 100 MIU for 8 to 12 weeks was more effective than lower doses.

Intravesical Interferon alfa-2b: TCC Prophylaxis

Study	No.	IFN-α2b Dose, MIU	Recurrence Rate, %	TTF, Months	Median f/u, Months
Kostakopoulos, 1990	30	10	37	11 (mean)	(12 - 28)
Bartoletti, 1991	19	54*	21	10 (median)	23.8
Portillo, 1997	39	60	54	—	43

*IFN-α2a.

Kostakopoulos A, et al. *Eur Urol.* 1990;18:201-203. Bartoletti R, et al. *Anticancer Res.* 1991;11:2167-2170. Portillo J, et al. *Urology.* 1997;49:187-190.

The efficacy of intravesical IFN-α in preventing recurrence and progression of superficial bladder cancer following complete TUR has been evaluated in several studies.[21-26] Recurrence rates ranged from 21% to 60%, which are somewhat higher than the recurrence rates observed with BCG. Few randomized studies exist to adequately assess the long-term efficacy of intravesical IFN-α therapy. The randomized study by Portillo et al[22] showed trends toward a lower recurrence rate and prolonged disease-free interval in patients treated with IFN-α2b; however, the trial was not adequately powered.

Interferon alfa-2b: Activity for BCG Failures

Study	No. Patients	Tumor type	CR
Glashan, 1990	9	CIS	2*
Bubley	12	Ta/T1	3
Lamm	18	Ta/T1	3
Williams, 1996	34	CIS	5
Total	73		13 (18%)

*At 12 months.
Personal communication.
Glashan R, et al. *J Urol.* 1990;144:658-661. Williams R, et al. *J Urol.* 1996;155:494. Abstract.

The observation that intravesical IFN-α2b therapy has substantial activity in up to 20% of patients who failed BCG therapy is extremely encouraging and suggests that one important application of IFN-α2b is in the treatment of BCG failures. In 4 small studies summarized here, IFN-α2b produced a CR in 18% of patients who relapsed following BCG therapy. In the studies reported by Glashan et al[18] and Williams et al,[27] 2 of 9 (22%) and 5 of 34 (15%) IFN-α2b–treated patients, respectively, remained in CR at 12 months.

Interferon alfa-2b: Durability of Responses in Patients With CIS

Time, months	N = 34 CR	PR
3	13 (38%)	5 (15%)
6	9 (26%)	2 (6%)
9	8 (24%)	0
12*	5 (15%)	0

*1 relapse at 18 months, 4/5 remain without evidence of disease at 33+ months.
Williams R, et al. *J Urol.* 1996;155:494. Abstract.

The durability of responses to intravesical IFN-α2b in patients who failed BCG is shown here.[27] At 3 months, 13 of 34 (38%) patients had a CR and 5 (15%) patients had a partial response (PR). Although the PRs were not durable beyond 6 months, nearly half of the CRs were durable for ≥1 year, and 12% of patients remain in CR at 33+ months (R Neri, personal communication, 1999).

Intravesical IFN-α: Toxicity

- Most common: flu-like symptoms , fever
- Incidence 0% to 19% in large studies
- No dose-limiting toxicity up to 1,000 MIU/dose
- Side effects easily controlled with nonsteroidal anti-inflammatory drugs

The advantage of intravesical IFN-α therapy is the excellent safety profile. Intravesical IFN-α is associated with minimal local toxicity. The most common adverse events are mild fever and flu-like symptoms, which occur in only a minority of treated patients. In large studies, >20% of patients have reported adverse events. In dose-ranging studies, no dose-limiting toxicity has been observed up to a dose of 1,000 MIU per instillation. Moreover, the side effects of intravesical IFN-α therapy are easily controlled with nonsteroidal anti-inflammatory drugs.

Combination Therapy: IFN-α2b Plus Chemotherapy

Study	No.	Drug	Dose*	Recurrence Rate, %	F/U, Months
Engelmann, ***1992	22	IFN-α2b	10 MIU	18	6.2 (mean)
	23	MMC	20 mg	22	6.2
	22	IFN-α2b + MMC	10 MIU/ 20 mg	0	6.2
Ferrari, ***1992	41	IFN-α2b	50 MIU	24	19 (median)
	44	IFN-α2b + EPI	50 MIU/ 80 mg	16	19

Engelmann U, et al. *Anticancer Drugs*. 1992;3(suppl 1):33-37.
Ferrari P, et al. *Anticancer Drugs*. 1992;3(suppl 1):25-27.

Clinical trials evaluating combinations of IFN-α plus mitomycin C (MMC) or epirubicin (EPI) have also suggested that these combinations may have additive or synergistic effects in the prophylaxis of superficial bladder cancer.[28-31] In one study by Englemann and colleagues, single-agent therapy with IFN-α2b or mitomycin C resulted in recurrence rates of 18% and 22%, respectively; however, there were no recurrences in the 22 patients treated with combination therapy.[28] A similar trial comparing 50 MIU IFN-α2b alone with rIFN-α2b plus 80 mg epirubicin did not demonstrate as large a difference; however, a slight advantage was noted with combination therapy.[29] All combination regimens were well tolerated.

Consensus 1995*: The Role of Intravesical IFN-α in Superficial Bladder Cancer

- Definite biologic activity against TCC
- Complete response rates are limited 25% to 40%
- Durability is uncertain
- Low toxicity: 20% to 30% mild flu-like symptoms
- Not recommended as a front-line agent but may be useful as a 2nd- or 3rd-line agent
- May have a role as part of a multidrug regimen

*Based on an advisory board meeting, San Francisco, Calif, 1995.

In summary, these studies demonstrate the biologic activity of IFN-α against superficial bladder cancer. Although CR rates are limited and durability is uncertain, IFN-α has substantial activity in patients who have failed BCG therapy. Toxicity is low; only 20% to 30% of patients experience mild flu-like symptoms. Therefore, while IFN-α is not recommended as front-line therapy, it clearly has utility as a second-line therapy, and it may play an important role in combination with other agents.

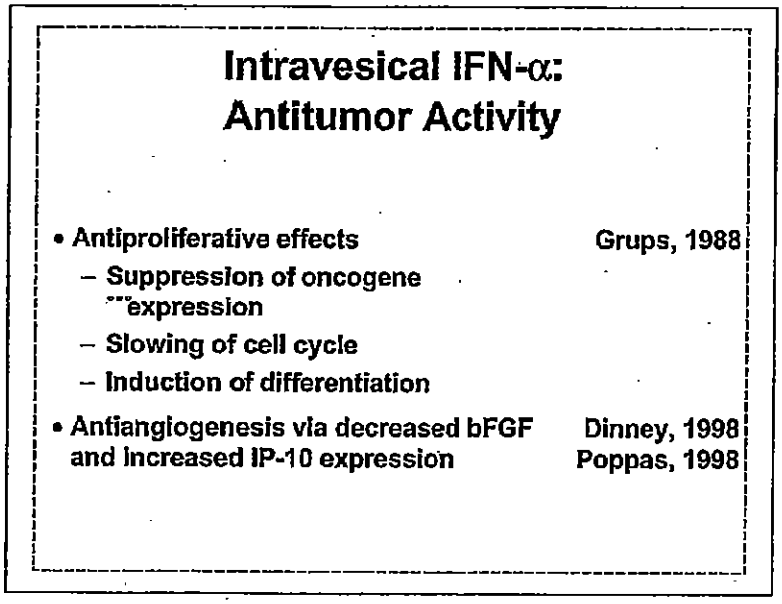
Mechanism of Action of IFN-α and BCG Against Superficial Bladder Cancer

Intravesical IFN-α: Immunomodulatory Effects

- Increased cytokine production from T cells and macrophages
  - Increased production of IFN-γ by PBMC — Molto, 1997
  - Increased production of IL-1β, IL-6, IL-8, GM-CSF, and TNF-α from bladder tumor cells — Zhang, 1999
- Increased NK cell activity in the bladder — Natsis, 1997
- Increased expression of antigens on TCC cells
  - IFN-α receptors — Giannopulos, 1997
  - MHC class II — Lattime, 1992
  - MHC class I and FAS — O Donnell, unpublished
- Increased lytic susceptibility of TCC — Tzai, 1992

Intravesical IFN-α has a variety of immunomodulatory effects in the bladder. It increases cytokine production, particularly interferon gamma (IFN-γ), from T cells and macrophages,[32] and increases the activity of natural killer (NK) cells in the bladder.[33] Interferon alfa also has effects on bladder tumor cells: IFN-α2b increased production of cytokines, namely interleukin-1beta (IL-1β), IL-6, IL-8, granulocyte–macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor alfa (TNF-α), by bladder cancer cell lines.[34] Increased expression of these cytokines correlated with cytotoxicity and growth inhibition. Interferon alfa also increases expression of cell surface antigens on bladder tumor cells that render them more susceptible to immune-mediated cytolysis.[35-37] In particular, IFN-α increases expression of major histocompatibility complex (MHC) antigens and FAS (O Donnel, unpublished data).[36] Expression of class II MHC antigens increases T-cell activation, whereas expression of class I MHC and FAS increases lysis by cytotoxic T cells expressing the FAS ligand.

Any 2000/2001 updates.
Any new data on antiangiogenesis.



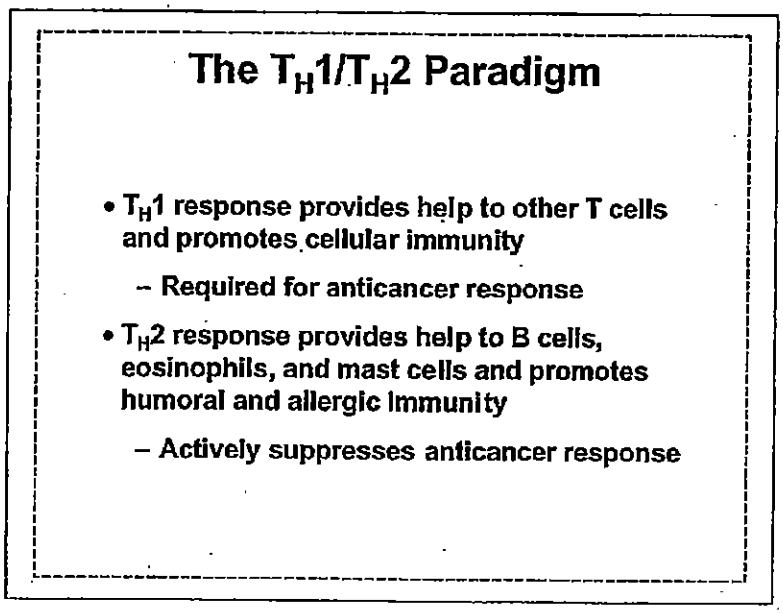
Intravesical IFN-α also has direct antitumor activity. Interferon alfa inhibited proliferation of bladder tumor cell lines in vitro by suppressing oncogene expression, slowing the cell cycle, and inducing differentiation.[38-40] Interferon alfa has also been shown to have antiangiogenic activity, which appears to be mediated by decreased expression of basic fibroblast growth factor (bFGF) on tumor cells and/or increased expression of the chemokine known as interferon-inducible protein 10 (IP-10) in the bladder;[41,42] IP-10 induces expression of other antiangiogenic cytokines such as IFN-γ and IL-12.[42]

Intravesical BCG: Antitumor Activity

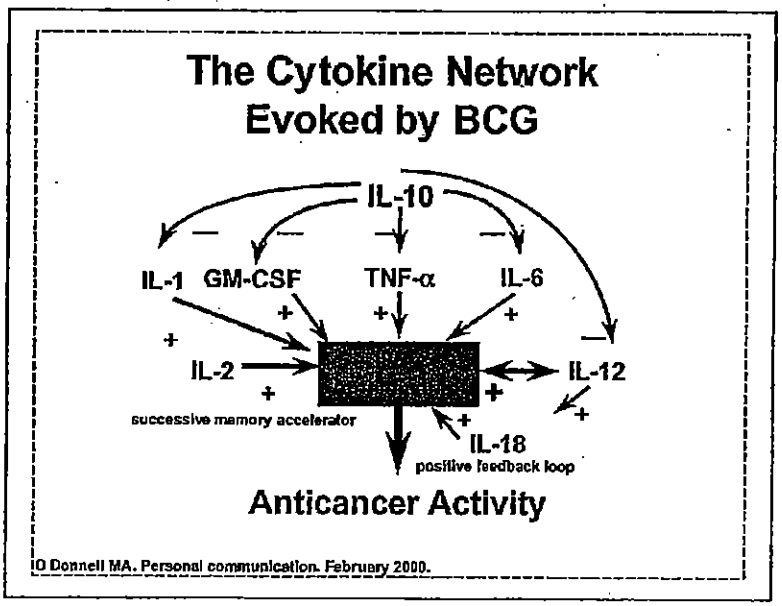
- Induces inflammatory response
- Induces infiltration of lymphocytes and NK cells into the bladder wall
- Induces complex cellular immune response characterized by release of the following cytokines:
  - IL-1
  - IL-2
  - IL-6
  - IL-8
  - IL-10
  - IL-12
  - IFN-γ
  - TNF-α
  - GM-CSF

Intravesical BCG also has a variety of immunomodulatory effects. BCG induces an inflammatory response in the bladder that induces infiltration of lymphocytes and NK cells into the bladder wall.[43,44] The complex cellular immune response initiated by BCG causes the secretion of a host of cytokines by T cells as well as bladder tumor cells. These cytokines work in concert to amplify the antitumor immune response.[43-45]

Changeover Slide



The cellular immune response can be directed by the local cytokine milieu toward either a T helper type 1 (T_H1) or a T helper type 2 (T_H2) response. T_H1 cells promote a cellular immune response that is mediated by cytotoxic T cells and NK cells and is responsible for the anticancer activity of the immune system. In contrast, T_H2 cells promote a humoral (antibody-mediated) and allergic immune response. The T_H2 response actively suppresses the anticancer immune response. Therefore, it is critical that immunotherapy promotes the T_H1 cellular immune response and not the T_H2 immune response.

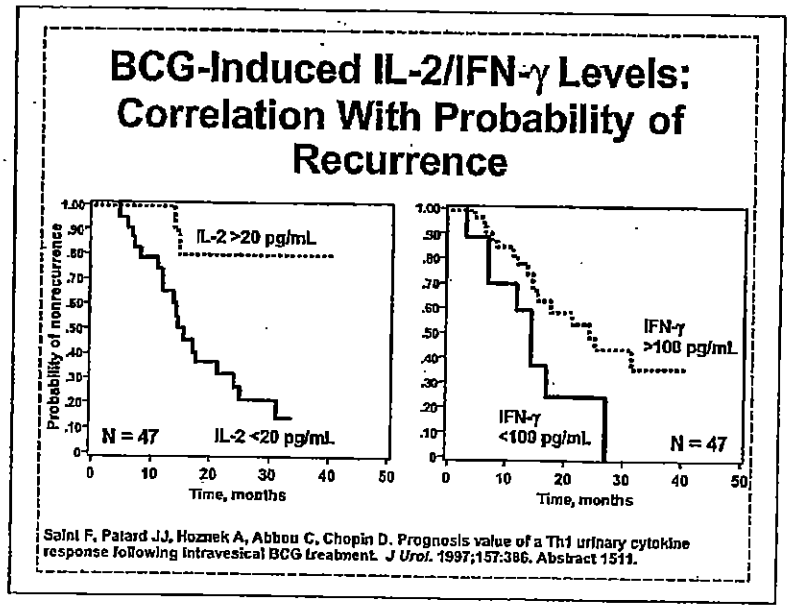


A host of cytokines produced in the bladder by T_H1 cells and macrophages work in concert to amplify production of interferon gamma (IFN-γ), which stimulates cytotoxic T cells and promotes the anticancer activity of the cellular immune response, up-regulates class II human leukocyte antigens (HLA) on bladder cancer cells, and has direct antiproliferative effects on bladder cancer cells.[46-48] In contrast, IL-10 produced by T_H2 cells as well as tumor cells suppresses the production of T_H1 cytokines.[49] The interplay between these competing cytokine networks can determine how vigorous the anticancer immune response will be. Immunotherapy aims to augment production of those cytokines that will boost the anticancer immune response. As previously discussed, BCG and IFN-α can both increase expression of T_H1 cytokines and amplify production of IFN-γ.

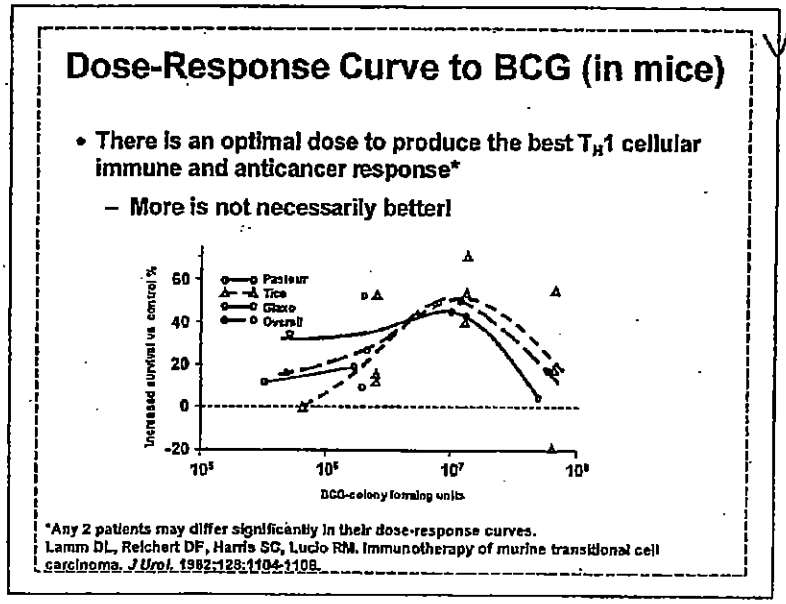
IFN-γ Is a Barometer of the T_H1 Immune Response

- Most dominant BCG-induced urinary cytokine; levels associated with clinical response
- Required for successful BCG immunity
- Marker of T_H1 activation (cellular immunity)
- Direct activity against bladder cancer cells
  - Decreases proliferation but not directly cytotoxic
  - Increases immunogenicity of TCC
  - Enhances apoptosis of TCC cells
- Potentially very useful surrogate marker

Interferon gamma is the dominant cytokine produced in the bladder in response to BCG therapy and appears to be a surrogate marker for a successful BCG-induced anticancer immune response. Although IFN-γ is not directly cytotoxic, it does have direct effects on bladder cancer cells: it has antiproliferative effects,[48] and it up-regulates expression of class II HLA antigens on bladder cancer cells.[46,47] Increased HLA-DR expression then stimulates T-cell activation. Interferon gamma can also enhance apoptosis of bladder cancer cells.

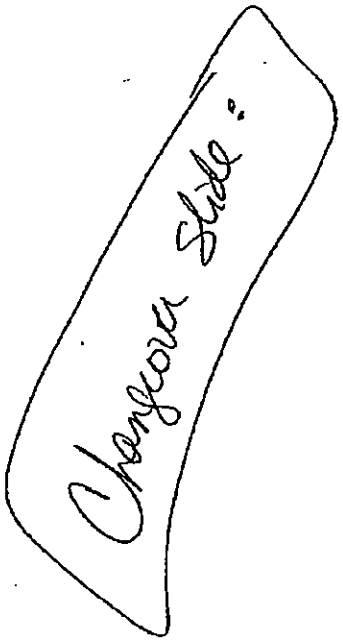


Peek urinary levels of interleukin-2 (IL-2) and IFN-γ in response to BCG correlate with the probability of response and recurrence.[50,51] The probability of remaining free of recurrence was higher in patients with urinary IL-2 levels > 20 pg/mL compared with lower levels (< 20 pg/mL).[51] Likewise, the probability of remaining free of recurrence was higher in patients with urinary IFN-γ levels > 100 pg/mL compared with lower levels (< 100 pg/mL). These data suggest that levels of these cytokines are surrogate markers of a vigorous immune response to BCG antigens, which correlates with eradication of residual tumor cells.



The antitumor response induced by various strains of BCG in mice is proportional to the dose of BCG, and the dose-response curve is bell shaped, indicating that there is an optimal dose to produce the best T_H1 cellular immune and anticancer response.[52] In this study, mice were inoculated intradermally with murine bladder tumor (MBT2) cells and then treated intralesionally with various doses of 3 different strains of BCG (Pasteur, Tice, and Glaxo). Tumor growth rate and survival were assessed. The curves represent the proportion of BCG-treated animals that survived versus control animals. The lesson from these in vivo experiments is that more BCG is not necessarily better. Higher doses decreased the antitumor response. In the clinical setting, it is important to remember that patients will not all have exactly the same dose-response curve.

Note: Pasteur + Tice FDA approved + equally effective


Overview Slide

Clinical Studies of BCG Dose Reduction

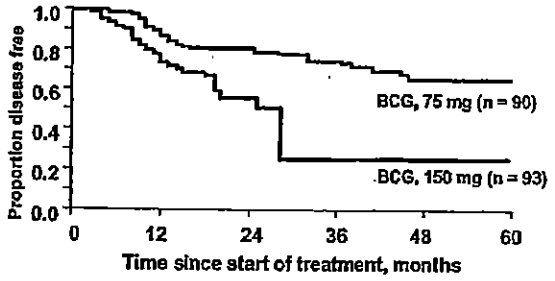
Study	N	Tumor Type	Dose	Disease Free, %	F/U, Mos
Pagano, 1991	63	Ta, T1	0 (control)	17	21 (median)
	74	Ta, T1	75 mg (1/2)*	74	
	56	CIS	75 mg	57	
Morales, 1992	48	Mixed	120 mg*	67	21 (median)
	49		60 mg (1/2)	37	
Martinez, 1995	252	Ta, T1	81 mg	82	19 (mean)
	248		27 mg (1/3)	80	
Hurle, 1996	51	T1 grade 3	75 mg (1/2)*	55	33 (median)

*Pasteur strain.
Connaught strain.

Several studies have investigated the activity and tolerability of reduced doses of BCG in patients with superficial bladder cancer. There is generally less toxicity with reduced does of BCG. Therefore, if the BCG dose could be lowered without sacrificing efficacy, then toxicity could be reduced. In general, these studies have shown that reduced doses of BCG appeared to be as effective as the standard dose. Pagano et al[53] investigated the activity of 75 mg Pasteur strain (1/2 the standard dose) for prophylaxis of Ta/T1 papillary tumors or treatment of CIS and found that this dose was effective. Hurle et al[54] reported similar results when patients with grade 3 T1 tumors were treated with 75 mg Pasteur strain. Martinez et al[55] conducted a large randomized trial comparing the activity of 1/3 dose (27 mg) of the Connaught strain with the standard 81-mg dose and demonstrated equivalent efficacy in terms of recurrence rate and progression rate. Notably, the group that received 27 mg BCG had significantly less severe local toxicity and systemic toxicity compared to the group that received 81 mg BCG ($P < .01$). The only negative results were reported by Morales et al.[56] In this study comparing 120 mg versus 60 mg Pasteur strain in patients with mixed tumor types, the 60-mg dose was less effective than the higher dose.

2001 EORTC 1/4 dose BCG.
Mack Jurol.

Low-Dose Versus High-Dose BCG



Study	N	Tumor Type	Dose	Disease Free, %	Median F/U, Mos
Pagano, 1995	93	Mixed	150 mg*	27	48
	90		75 mg ($^1/_2$)	66	

*Pasteur strain.

Pagano F, et al. *Eur Urol*. 1995;27(suppl 1):19-22.

The most positive results achieved with reduced doses of BCG were reported by Pagano et al.[57] In this randomized phase III trial, patients treated with 75 mg Pasteur strain had a significantly higher response rate than patients treated with 150 mg (P = .0009). Moreover, with a median follow-up of 48 months, 66% of patients treated with 75 mg BCG remained disease free compared with only 27% of patients in the 150-mg group. The incidence of the most severe local and systemic toxicities (cystitis, fever, and hematuria) was significantly reduced in the 75-mg dose group. No difference in progression rate was observed between treatment groups.

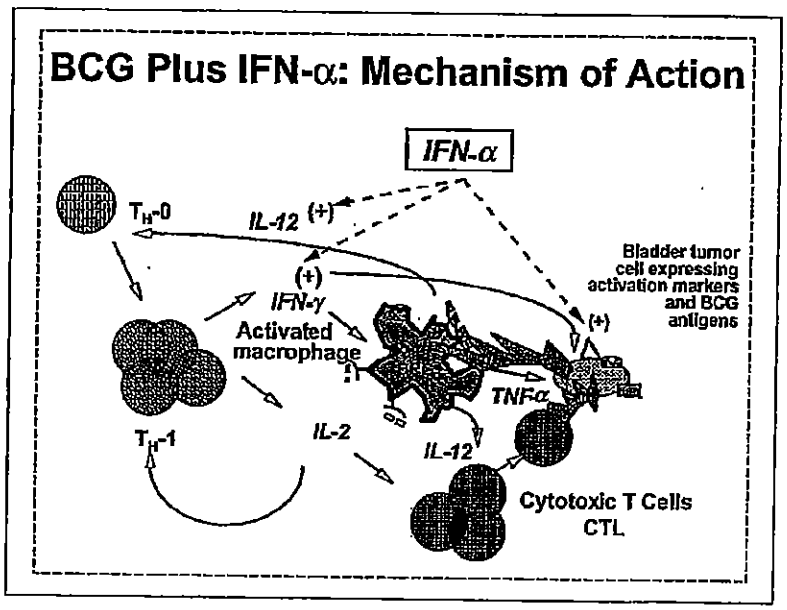
Combination Therapy: Interferon alfa-2b Plus BCG

Based on the available data, there is a strong clinical rationale for combination therapy with interferon alfa-2b plus BCG. This section reviews the clinical rationale for combination therapy and presents some preliminary clinical data.

BCG Plus IFN-α Combination Therapy: Rationale

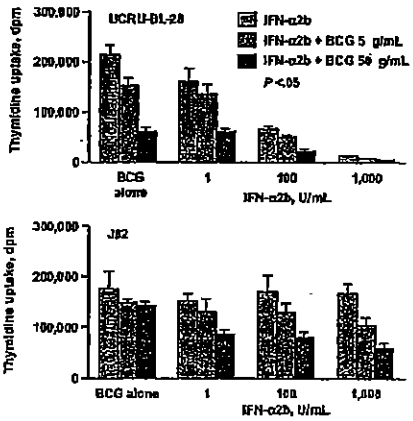
- Evidence of synergistic activity
  - Accentuates the T_H1 cytokine response
- Recombinant interferon alfa and BCG have complementary biologic activities
  - Infiltration of lymphocytes and NK cells to bladder (BCG)
  - Increased HLA expression on TCC cells (IFN-α)
  - Increased cytolytic activity of cytotoxic T cells (IFN-α)
- Recombinant interferon alfa and BCG are biocompatible
- Reduced dose of BCG may reduce toxicity while maintaining efficacy

As we have discussed, the biologic activities of IFN-α and BCG are complementary.[43,45] They appear to collaborate to accentuate the T_H1 cellular immune response,[58] and there is evidence that they may have synergistic activity. BCG stimulates infiltration of lymphocytes and NK cells into the bladder wall,[43,44] while IFN-α serves to up-regulate the cellular immune response. Interferon alfa increases human leukocyte antigen (HLA) expression of bladder cancer cells, rendering them more susceptible to cytotoxic T cells (CTLs), and increases the cytolytic activity of CTLs.[36] Moreover, BCG and IFN-α are biocompatible and can be instilled simultaneously into the bladder.[59] By combining IFN-α with a reduced dose of BCG, toxicity can be reduced while maintaining anticancer efficacy.



The mechanism of action of intravesical BCG plus IFN-α in patients with bladder cancer is illustrated here. BCG antigens are taken up by macrophages and other antigen-presenting cells and presented to T cells, which stimulates a cellular immune response. The BCG-activated macrophages produce cytokines, including IL-12 and TNF-α. Interleukin-12 plays a dominant role in the induction of IFN-γ production,[60] whereas TNF-α has direct antitumor activity. Activated T_H1 cells produce IL-2 and IFN-γ both of which have been shown to correlate with clinical response.[50,51] Exogenous intravesical IFN-α augments the production of IFN-γ by T_H1 cells, which in turn enhances BCG antigen presentation and further amplifies the cellular immune response. Intravesical IFN-α also up-regulates HLA and FAS expression on the bladder cancer cells, which increases presentation of BCG antigens by tumor cells and enhances tumor cells lysis by activated CTLs.[36] The end result is an effective anticancer immune response.

BCG Plus IFN-α2b: Synergistic Antiproliferative Effects on TCC Cells In Vitro



Pryor K, et al. *Cancer Immunol Immunother.* 1995;41:309-316.

In addition to these synergistic immunomodulatory activities, in vitro studies have shown that BCG and IFN-α2b also have synergistic antiproliferative effects on bladder cancer cell lines. In these experiments, 2 different cell lines were incubated with either BCG alone at 2 doses (5 and 50μg/mL), IFN-α2b alone at 3 doses (1,100 and 1,000 U/mL), or IFN-α2b plus BCG.[61] Both BCG and IFN-α2b alone had dose-dependent antiproliferative effects on the UCRU-BL-28 cell line; however, the combination had dramatically greater dose-dependent effects on the proliferation of this cell line. Likewise, although the J82 cell line did not appear to be sensitive to either BCG or IFN-α2b alone, the combination of BCG plus IFN-α2b had a dramatically greater antiproliferative effect than either agent alone.

BCG Plus IFN-α: ~~Summary of~~ Experimental Results

- Amplifies T_H1 cytokine response
  - Increases IFN-γ production 15- to 40-fold
- Suppresses T_H2 cytokine response (IL-10)
- Broadens the bell shaped dose response curve of BCG; can reverse some T-cell anergy
- Super-additive direct antitumor effects
  - Antiproliferative effects
  - Antiangiogenic effects
  - Increased tumor immunogenicity

In summary, the experimental results with the combination of BCG and IFN-α indicate that this combination has potent immunomodulatory effects. Together, BCG and IFN-α amplify the T_H1 cellular immune response by increasing IFN-γ production by 15- to 40-fold, while simultaneously suppressing the T_H2 cytokine response, which is characterized by IL-10 secretion. The combination of BCG and IFN-α also appears to broaden the bell-shaped dose-response curve associated with BCG, possibly by reversing some T-cell anergy. Finally, these 2 agents appear to have super-additive direct effects on tumors; they appear to have antiproliferative and antiangiogenic effects, and they increase tumor immunogenicity.

BCG Plus IFN-α2b: Published Clinical Trials

Study	No.	Tumor Type	Regimen	Dose	Outcome	Median FU, mo
Stricker, 1996	7	CIS	IFN-α2b + ½-dose BCG*	10 - 100 MIU 60 mg	86% CR	12
	6	pTCC	IFN-α2b + ½-dose BCG	10 - 100 MIU 60 mg	50% NED, 40% PR	12
Bercovich, 1995	18	pTCC	full-dose BCG*	120 mg	RR = 28%	24
	18		IFN-α2b + ½-dose BCG	10 MIU 60 mg	RR = 22%	17
O Donnell, 2000	27	Mixed, high risk	IFN-α2b + ⅓-dose BCG	50 MIU 27 mg	59% NED	16

*Pasteur strain.
Connaught strain.
NED = No evidence of disease; RR = Recurrence rate.

Stricker P, et al. *Urology*. 1996;48:357-361. Bercovich E, et al. *Arch Ital Urol Androl*. 1995;67:257-260. O Donnell M, et al. *J Urol*. 2000;163 (suppl):152. Abstract 676.

Final publication

Based on this sound clinical rationale, a number of centers have investigated the combination of BCG plus IFN-α2b in patients with superficial bladder cancer. Data from 3 clinical studies suggest that IFN-α2b plus BCG may be superior to either agent alone, and may allow reduction of the BCG dose without compromising antitumor efficacy. In the study reported by Stricker et al,[62] combination therapy using 60 mg Pasteur strain (1/2 dose) was well tolerated and produced favorable response rates in patients with papillary tumors and CIS. The randomized trial reported by Bercovich et al[63] demonstrated that combination therapy with IFN-α2b (10 MIU) plus 1/2 dose BCG (Pasteur strain) yielded a lower rate of recurrence compared with full-dose BCG (22% versus 28%) and was associated with fewer BCG-related adverse events.

In a preliminary report by O Donnell et al,[64] 16 of 27 (59%) high-risk patients treated with 27 mg Connaught strain (1/3 dose) plus 50 MIU IFN-α2b, had no evidence of disease with a median follow-up of 16 months. Updated results of this study, with 52 patients evaluable at a median follow-up of 14 months, have shown a disease-free rate of 67% at 1 year and 53% at 2 years (MA O Donnell, unpublished data). Most significantly, 56% of patients who had failed prior BCG therapy (up to 3 courses) were disease-free at 2 years.[65]

BCG Plus IFN-α2b: Ongoing Randomized Trials

Study	No.	Tumor Type	Regimen	Dose	Recurrence Rate	Median F/U, Mo
O Donnell, [66] 1999	38	pTCC CIS	IFN-α2b + BCG*	50 MIU/ 81 mg	2/19 (11%)	18
			vs			
			Full-dose BCG	81 mg	6/19 (32%)	
Esuvaranathan, [66] 2000	80	pTCC CIS	IFN-α2b + 1/3 BCG*	10 MIU/ 27 mg	10%	19
			vs			
			1/3-dose BCG	27 mg	30%	
			vs			
			Full-dose BCG	81 mg	50%	

*Connaught strain.

O Donnell MA. Unpublished data. 1999. Esuvaranathan K, et al. *J Urol.* 2000;163(suppl):152. Abstract 675.

Final update

Add new data

Two on-going prospective randomized trials are comparing the efficacy of combination therapy with that of single-agent (full- or reduced-dose) BCG. A double-blind pilot study is being conducted at Boston s Beth Israel Deaconess Medical Center (BIDMC) in patients with aggressive superficial bladder cancer (grade 3 Ta or T1 tumors or CIS) who have not been previously treated with BCG. Preliminary results of this study suggest that the combination of IFN-α2b (50 MIU) plus full-dose BCG (81 mg Connaught strain) is superior to 81 mg BCG alone. With a median follow-up of 18 months, only 2 of 19 (11%) patients treated with IFN-α2b plus BCG have relapsed compared with 6 of 19 (32%) patients treated with BCG alone (MA O Donnell, unpublished data, 1999). In an ongoing randomized phase IIB trial in Singapore, the combination of IFN-α2b (10 MIU) plus 1/3 dose BCG (27 mg Connaught strain) produced the lowest recurrence rate at a median follow-up of 19 months (10% versus 30% and 50% with BCG alone).[66] Moreover, the incidence of BCG-associated adverse events (local and systemic) was significantly reduced ($P < .01$) in patients who received either reduced-dose BCG alone or the combination regimen. These studies strongly suggest a positive synergistic effect between BCG and IFN-α2b; however, a much larger, multi-center, randomized study is needed to confirm this.

Final update w/ pub data

BCG Plus IFN-α2b: BIDMC Study Design

- Induction
  - No prior BCG: BCG + IFN-α2b (50 MIU) × 6-8 wks
  - BCG failures: $^1/_3$-dose BCG + IFN-α2b (50 MIU) × 6-8 wks
  - BCG intolerant or BCG + IFN-α relapsed: $^1/_{10}$ BCG + IFN-α2b (100 MIU) × 6 wks
- Maintenance
  - 3 cycles of 3 installations @ 3, 9, 15 months after end of induction
  - Dose $^1/_3$ - $^1/_{10}$ BCG + IFN-α2b (50-100 MIU)
- Further dose reduction (and delay) for intolerance
  - Lowest BCG dose $^1/_{100}$th standard dose
  - IFN-α2b dose never reduced
- Follow-up every 3-4 months by cystology, cytology, and biopsy

O Donnell MA. Personal communication. December 1999.

Based on the encouraging results of the pilot study described in the previous slide, an open-label trial of BCG plus IFN-α2b is currently being conducted at BIDMC to compare the activity of 3 different regimens (MA O Donnell, personal communication, 1999). In this trial, all patients are receiving combination induction therapy with (50 or 100 MIU) plus BCG at 3 different doses for 6 to 8 weeks. Patients who have not been previously treated with BCG are receiving full-dose BCG plus 50 MIU IFN-α2b; patients who have failed prior BCG therapy are receiving 1/3-dose BCG plus 50 MIU IFN-α2b; and patients who are unable to tolerate BCG are receiving 1/10-dose BCG plus 100 MIU IFN-α2b. Responding patients are receiving combination maintenance therapy at 3-month intervals. If toxicity becomes dose-limiting, the BCG dose is further reduced, but the IFN-α2b. Responding patients are receiving combination maintenance therapy at 3-month intervals. If toxicity becomes dose-limiting, the BCG dose is further reduced, but the IFN-α2b is maintained. Patients are being followed every 3 to 4 months by cystology, cytology, and biopsy as needed.

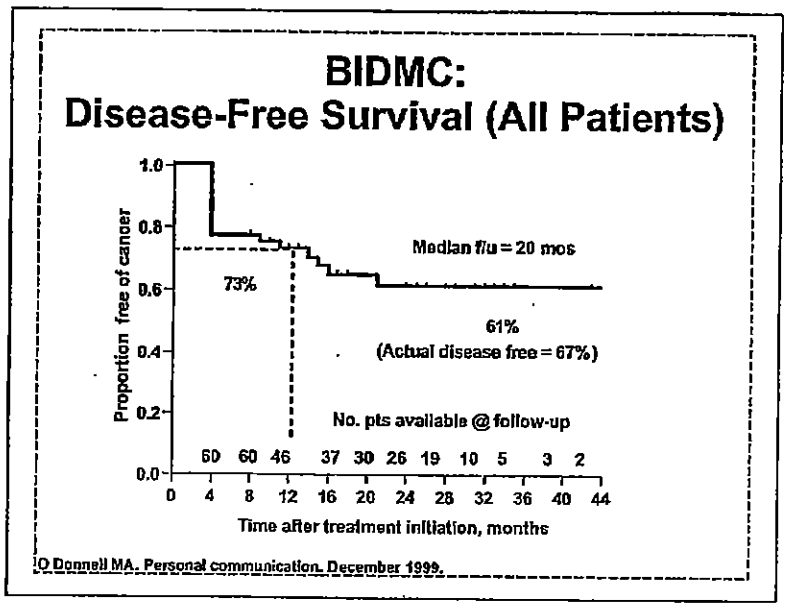
talk to Mr O'Donnell to see what he is willing to do for this section.

BIDMC: Patient Profile (12/99)

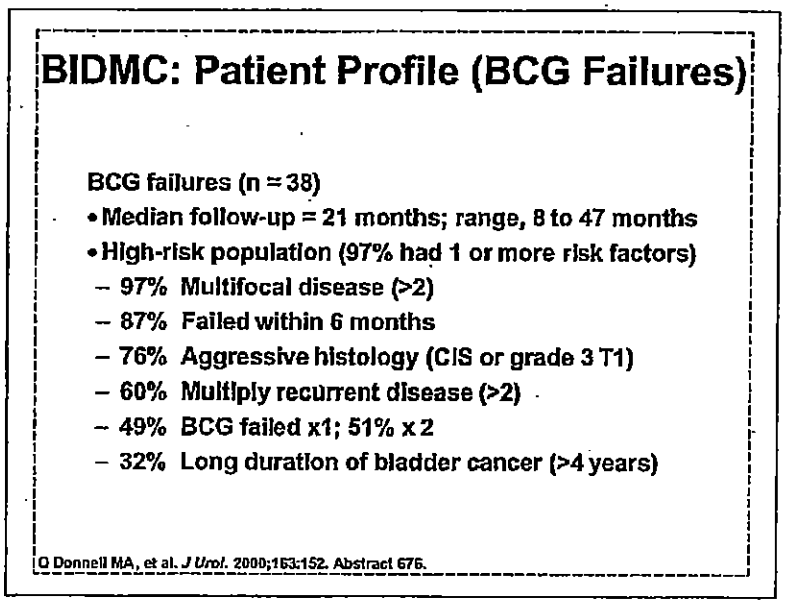
- N = 68 (60 patients evaluable)
- Median f/u = 21 months; range, 8 to 47 months
- High-risk population (98% had 1 or more risk factors)
  - 93% Multifocal disease (>2)
  - 78% Residual disease present at treatment start (CIS — 67% orpTCC — 12%)
  - 75% Aggressive histology (CIS or grade 3 T1)
  - 56% Prior BCG failures (1-3 cycles)
  - 55% Multiply recurrent disease (>2)
  - 27% Long duration of bladder cancer (>4 yrs)

O Donnell MA. Personal communication. December 1999.

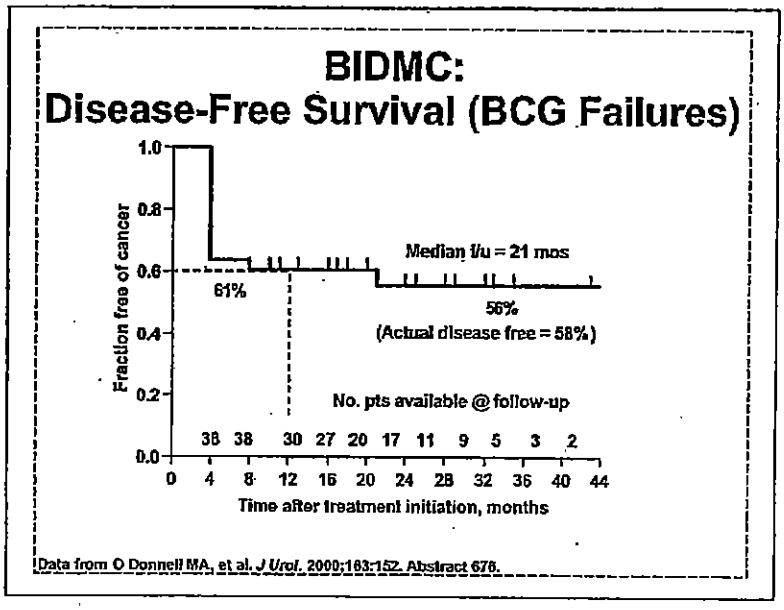
As of December 1999, 68 patients had been enrolled in the BIDMC trial, and 60 patients were evaluable. The median follow-up as of this date was 21 months. The vast majority (98%) of patients enrolled in this trial are at a high risk of recurrence as a result of having 1 or more of these risk factors. Nearly all (93%) of patients had multifocal disease, most (78%) patients had residual disease at the start of treatment (67% residual CIS and 12% residual papillary tumors), and most (75%) patients had aggressive histology (either CIS or grade III T1 tumors). In addition, 38 (56%) patients had failed 1 to 3 prior cycles of BCG therapy, and more than half (55%) of patients had more than 2 prior recurrences. Finally, 27% of patients had bladder cancer for > 4 years prior to entry in this trial.



Among evaluable patients, 73% of patients had no evidence of disease at 1 year from the start of treatment, and 61% of patients had no evidence of disease at 2 years. With a median follow-up of 20 months as of December 1999, the disease-free survival curve appears to have reached a plateau with some patients remaining disease free well beyond 2 years. The majority of recurrences were observed at the first follow-up evaluation.



Within this cohort of 68 patients, 28 (56%) patients had failed prior BCG therapy. The median follow-up as of December 1999 in this group of patients was 21 months.[65] The profile of patients who had failed BCG was similar to the larger study population. The vast majority (97%) of these patients had 1 or more risk factors for recurrence. Nearly all (97%) had multifocal disease, and 87% had failed prior therapy within 6 months.



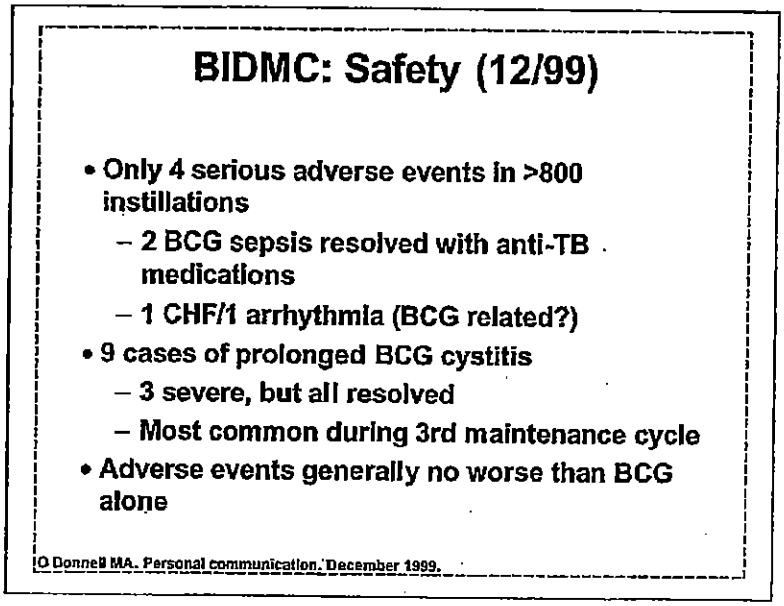
Among the BCG failures, 61% of patients had no evidence of disease at 1 year from the start of treatment, and 56% of patients remain disease free at 2 years and beyond.[65] This low rate of recurrence is extremely encouraging among this group of patients. The majority of failures occurred within the first 4 months and were observed at the first follow-up evaluation, thus permitting early radical cystectomy. Beyond that point there have been very few recurrences.

BIDMC: Other Observations (BCG Failures)

- 12/20 (60%) patients told to consider cystectomy are disease free with a normal functioning bladder
- 13/15 (87%) of BCG failures occurred within the first 4 months (at first cystoscopy)
- 4/11 (36%) of BCG/IFN-α2b failures became disease free with a second course
- Previous refractory BCG di sease (ie, relapse or no response by 6 months) was NOT a poor prognostic indicator
- Patients who failed BCG twice did just as well as those who had failed BCG only once

O Donnell MA. Personal communication. December 1999.

Within the group of patients in the BIDMC trial who had failed prior BCG therapy, several other observations are noteworthy: among those patients who were told by their physician to consider cystectomy, 60% achieved a CR to combination therapy with IFN-α2b plus BCG and have a normal functioning bladder today; 87% of BCG failures occurred within 4 months of treatment initiation (in fact, a similar trend was observed with respect to recurrences following combination therapy in this trial); 36% of patients who recurred following combination therapy achieved a CR to a second course of therapy; and patients who were refractory to prior BCG therapy responded just as well to combination therapy as patients who had previously responded to BCG and then relapsed. Therefore, BCG refractory disease is not a poor prognostic factor for response to IFN-α2b plus BCG. Finally, patients who had multiple recurrences following BCG therapy did just as well on combination therapy as patients who had failed only 1 previous course of BCG.



Combination therapy with IFN-α2b plus BCG (full or reduced dose) was safe and well tolerated. There were only 4 serious adverse events in over 800 instillations. Two patients developed BCG sepsis that resolved with treatment, and 1 patient each developed congestive heart failure (CHF) and arrhythmia, which may or may not have been treatment related. There were also 9 cases of prolonged cystitis, 3 of which were severe, but all resolved. Cystitis most often occurred during the 3rd maintenance cycle. The adverse events profile of combination therapy was generally no worse than BCG alone, and patients who received reduced doses of BCG had fewer adverse events.

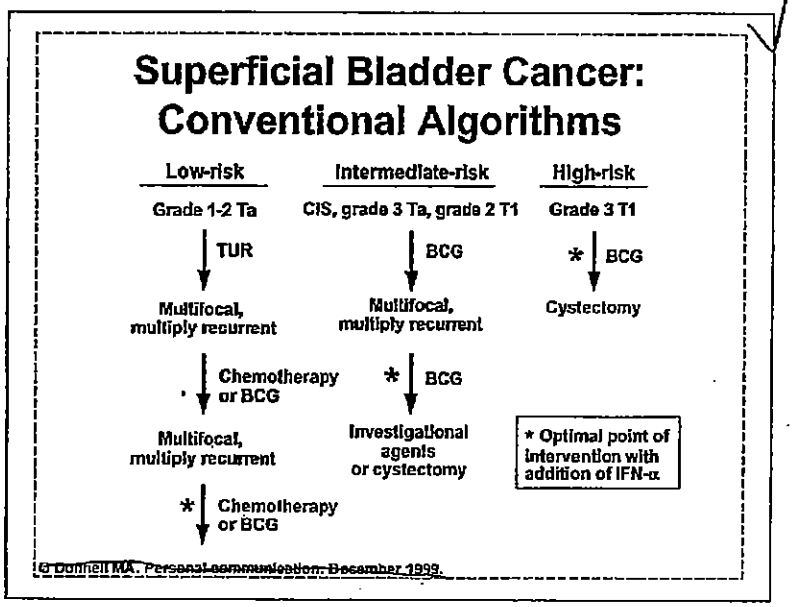
BIDMC: Conclusions

- BCG plus IFN-α2b is a safe form of intravesical therapy
- Combination therapy appears to have excellent anticancer efficacy even in cases of prior BCG failure
- Dose reduction and treatment delay in BCG is possible in combination therapy without apparent decrease in efficacy
- Larger controlled trials are needed to validate the potential of combination therapy

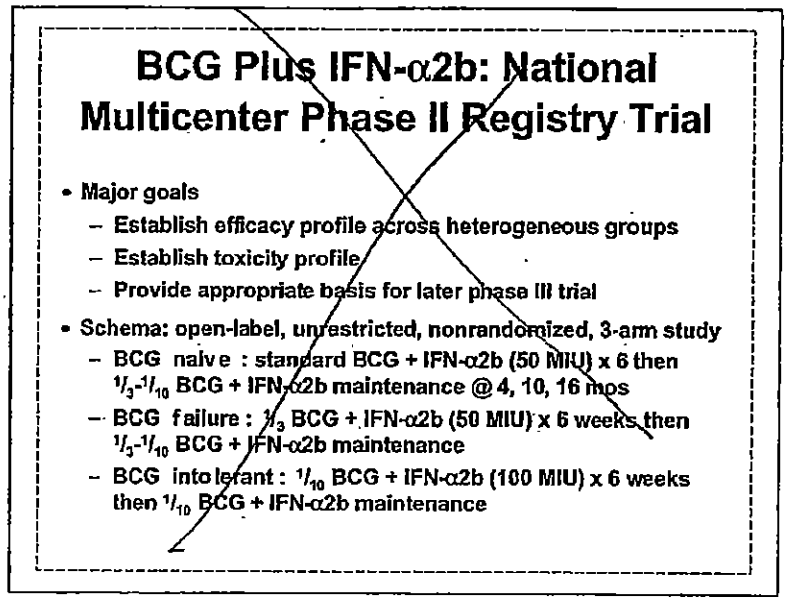
O'Donnell MA. Personal communication. December 1999.

In conclusion, the preliminary results of this open-label trial being conducted at BIDMC suggest that the combination of IFN-α2b plus BCG is safe and appears to be highly effective even in patients who have failed prior BCG therapy. With combination therapy it is also possible to reduce or delay the BCG dose without any apparent decrease in efficacy. Although these results are promising, larger controlled trials are needed to validate the efficacy of combination therapy.

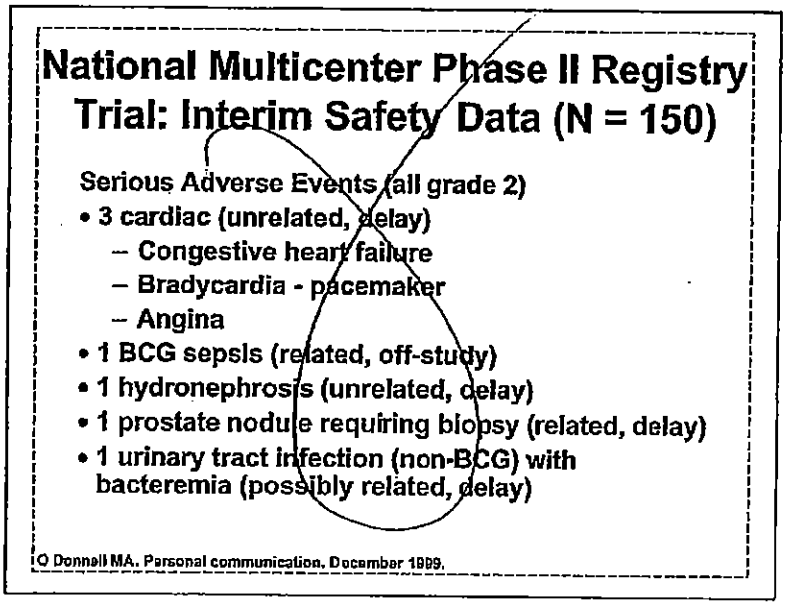
add slide on Kleen trial



Based on the available data with regard to the activity and utility of IFN-α in the treatment of superficial bladder cancer, there are several points in the conventional disease management algorithm where IFN-α might optimally be integrated. In patients with low-grade Ta tumors and multifocal disease or multiple recurrences, chemotherapy or BCG may be the most appropriate first-line intravesical therapy; however, combination therapy should be considered if the disease continues to recur. Patients with intermediate-risk disease (ie, CIS or high-grade papillary tumors) are usually treated with BCG as first-line adjuvant intravesical therapy. However, if these patients have multifocal disease or multiple recurrences, then combination therapy should be considered prior to investigational agents or cystectomy. Finally, in patients with high-risk disease, combination therapy with IFN-α plus BCG should be considered as first-line intravesical therapy prior to cystectomy.



To validate the activity of combination therapy with IFN-α2b plus BCG in superficial bladder cancer, a national multicenter phase II open-label registry trial has been initiated. The goals of that trial are to establish the efficacy of combination therapy across heterogeneous groups of patients, to establish the tolerability profile, and to provide a clinical basis for phase III trials. This trial will follow a similar schema as the open-label BIDMC trials previously described. The dose of BCG and IFN-α2b will vary depending on whether the patient is BCG naive, has failed prior BCG therapy, or is intolerant to BCG.



As of December 1999, 150 patients had been enrolled in this trial. Interim safety data are favorable. There have been only 7 serious adverse events reported: 3 cardiac events; 1 case of BCG sepsis; 1 case of hydronephrosis; 1 case of prostate nodule; and 1 case of a bacterial urinary tract infection that was not BCG. The cardiac events were considered unrelated to treatment, but required treatment delay. The 1 patient with BCG sepsis went off study; all other patients remained on the study but had treatment delays. These data demonstrate the favorable tolerability profile of combination therapy in a large cohort of patients. Interim efficacy data from this trial will likely be available within the next year.

Combination Therapy: Conclusions

- BCG and IFN-α have synergistic immunomodulatory and antitumor activity (enhance the T_H1 response)
- In open-label trials, BCG + IFN-α2b was well tolerated and allowed BCG dose reductions without compromising efficacy
- BCG + IFN-α2b is effective in patients who have failed 1 or more previous courses of BCG
- Combination therapy ~~should~~ may be considered prior to radical cystectomy in high-risk patients
- Randomized, controlled trials are ~~needed~~ being underway

In conclusion, the preclinical and clinical data suggest that BCG and IFN-α have complementary and potentially synergistic immunomodulatory and antitumor activity. They enhance the T_H1 cellular immune response and potentiate IFN-γ production. Open-label trials have demonstrated that combination therapy is well tolerated and allows BCG dose reductions without compromising antitumor efficacy in patients with superficial bladder cancer. Moreover, BCG plus IFN-α2b is effective in patients who have failed 1 or more previous courses of BCG therapy. Therefore, BCG should be considered in high-risk patients with multiple recurrent multifocal disease prior to radical cystectomy. Future randomized trials will be needed to validate the activity of combination therapy compared with standard BCG therapy.

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Form **W-9**
(Rev. December 2000)
Department of the Treasury
Internal Revenue Service

Request for Taxpayer Identification Number and Certification

Give form to the requester. Do not send to the IRS.

Please print or type

Name (See Specific Instructions on page 2.)

Business name, if different from above. (See Specific Instructions on page 2.)

Check appropriate box: ☐ Individual/Sole proprietor ☐ Corporation ☐ Partnership ☐ Other ▶

Address (number, street, and apt. or suite no.)

Requester's name and address (optional)

City, state, and ZIP code

Part I Taxpayer Identification Number (TIN)

Enter your TIN in the appropriate box. For individuals, this is your social security number (SSN). However, for a resident alien, sole proprietor, or disregarded entity, see the Part I instructions on page 2. For other entities, it is your employer identification number (EIN). If you do not have a number, see How to get a TIN on page 2.

Note: *If the account is in more than one name, see the chart on page 2 for guidelines on whose number to enter.*

Social security number

or

Employer identification number

List account number(s) here (optional)

Part II For U.S. Payees Exempt From Backup Withholding (See the instructions on page 2.)

▶

Part III Certification

Under penalties of perjury, I certify that:

1. The number shown on this form is my correct taxpayer identification number (or I am waiting for a number to be issued to me), and
2. I am not subject to backup withholding because: (a) I am exempt from backup withholding, or (b) I have not been notified by the Internal Revenue Service (IRS) that I am subject to backup withholding as a result of a failure to report all interest or dividends, or (c) the IRS has notified me that I am no longer subject to backup withholding, and
3. I am a U.S. person (including a U.S. resident alien).

Certification instructions. You must cross out item 2 above if you have been notified by the IRS that you are currently subject to backup withholding because you have failed to report all interest and dividends on your tax return. For real estate transactions, item 2 does not apply. For mortgage interest paid, acquisition or abandonment of secured property, cancellation of debt, contributions to an individual retirement arrangement (IRA), and generally, payments other than interest and dividends, you are not required to sign the Certification, but you must provide your correct TIN. (See the instructions on page 2.)

Sign Here Signature of U.S. person ▶ Date ▶

Purpose of Form

A person who is required to file an information return with the IRS must get your correct taxpayer identification number (TIN) to report, for example, income paid to you, real estate transactions, mortgage interest you paid, acquisition or abandonment of secured property, cancellation of debt, or contributions you made to an IRA.

Use Form W-9 only if you are a U.S. person (including a resident alien), to give your correct TIN to the person requesting it (the requester) and, when applicable, to:

1. Certify the TIN you are giving is correct (or you are waiting for a number to be issued),
2. Certify you are not subject to backup withholding, or
3. Claim exemption from backup withholding if you are a U.S. exempt payee.

If you are a foreign person, use the appropriate Form W-8. See Pub. 515, Withholding of Tax on Nonresident Aliens and Foreign Corporations.

Note: *If a requester gives you a form other than Form W-9 to request your TIN, you must use the requester's form if it is substantially similar to this Form W-9.*

What is backup withholding? Persons making certain payments to you must withhold and pay to the IRS 31% of such payments under certain conditions. This is called "backup withholding." Payments that may be subject to backup withholding include interest, dividends, broker and barter exchange transactions, rents, royalties, nonemployee pay, and certain payments from fishing boat operators. Real estate transactions are not subject to backup withholding.

If you give the requester your correct TIN, make the proper certifications, and report all your taxable interest and dividends on your tax return, payments you receive will not be subject to backup withholding. Payments you receive will be subject to backup withholding if:

1. You do not furnish your TIN to the requester, or
2. You do not certify your TIN when required (see the Part III instructions on page 2 for details), or
3. The IRS tells the requester that you furnished an incorrect TIN, or
4. The IRS tells you that you are subject to backup withholding because you did not report all your interest and dividends on your tax return (for reportable interest and dividends only), or
5. You do not certify to the requester that you are not subject to backup withholding under 4 above (for reportable interest and dividend accounts opened after 1983 only).

Certain payees and payments are exempt from backup withholding. See the Part II instructions and the separate Instructions for the Requester of Form W-9.

Penalties

Failure to furnish TIN. If you fail to furnish your correct TIN to a requester, you are subject to a penalty of $50 for each such failure unless your failure is due to reasonable cause and not to willful neglect.

Civil penalty for false information with respect to withholding. If you make a false statement with no reasonable basis that results in no backup withholding, you are subject to a $500 penalty.

Criminal penalty for falsifying information. Willfully falsifying certifications or affirmations may subject you to criminal penalties including fines and/or imprisonment.

Misuse of TINs. If the requester discloses or uses TINs in violation of Federal law, the requester may be subject to civil and criminal penalties.

Specific Instructions

Name. If you are an individual, you must generally enter the name shown on your social security card. However, if you have changed your last name, for instance, due to marriage without informing the Social Security Administration of the name change, enter your first name, the last name shown on your social security card, and your new last name.

If the account is in joint names, list first and then circle the name of the person or entity whose number you enter in Part I of the form.

Sole proprietor. Enter your individual name as shown on your social security card on the "Name" line. You may enter your business, trade, or "doing business as (DBA)" name on the "Business name" line.

Limited liability company (LLC). If you are a single-member LLC (including a foreign LLC with a domestic owner) that is disregarded as an entity separate from its owner under Treasury regulations section 301.7701-3, enter the owner's name on the "Name" line. Enter the LLC's name on the "Business name" line.

Caution: *A disregarded domestic entity that has a foreign owner must use the appropriate Form W-8.*

Other entities. Enter your business name as shown on required Federal tax documents on the "Name" line. This name should match the name shown on the charter or other legal document creating the entity. You may enter any business, trade, or DBA name on the "Business name" line.

Part I—Taxpayer Identification Number (TIN)

Enter your TIN in the appropriate box.

If you are a resident alien and you do not have and are not eligible to get an SSN, your TIN is your IRS individual taxpayer identification number (ITIN). Enter it in the social security number box. If you do not have an ITIN, see How to get a TIN below.

If you are a sole proprietor and you have an EIN, you may enter either your SSN or EIN. However, the IRS prefers that you use your SSN.

If you are an LLC that is disregarded as an entity separate from its owner (see *Limited liability company (LLC)* above), and are owned by an individual, enter your SSN (or "pre-LLC" EIN, if desired). If the owner of a disregarded LLC is a corporation, partnership, etc., enter the owner's EIN.

Note: *See the chart on this page for further clarification of name and TIN combinations.*

How to get a TIN. If you do not have a TIN, apply for one immediately. To apply for an SSN, get Form SS-5, Application for a Social Security Card, from your local Social Security Administration office. Get Form W-7, Application for IRS Individual Taxpayer Identification Number, to apply for an ITIN or Form SS-4, Application for Employer Identification Number, to apply for an EIN. You can get Forms W-7 and SS-4 from the IRS by calling 1-800-TAX-FORM (1-800-829-3676) or from the IRS's Internet Web Site at www.irs.gov.

If you do not have a TIN, write "Applied For" in the space for the TIN, sign and date the form, and give it to the requester. For interest and dividend payments, and certain payments made with respect to readily tradable instruments, generally you will have 60 days to get a TIN and give it to the requester before you are subject to backup withholding on payments. The 60-day rule does not apply to other types of payments. You will be subject to backup withholding on all such payments until you provide your TIN to the requester.

Note: *Writing "Applied For" means that you have already applied for a TIN or that you intend to apply for one soon.*

Part II—For U.S. Payees Exempt From Backup Withholding

Individuals (including sole proprietors) are not exempt from backup withholding. Corporations are exempt from backup withholding for certain payments, such as interest and dividends. For more information on exempt payees, see the separate Instructions for the Requester of Form W-9.

If you are exempt from backup withholding, you should still complete this form to avoid possible erroneous backup withholding. Enter your correct TIN in Part I, write "Exempt" in Part II, and sign and date the form.

If you are a nonresident alien or a foreign entity not subject to backup withholding, give the requester the appropriate completed Form W-8.

Part III—Certification

To establish to the withholding agent that you are a U.S. person, or resident alien, sign Form W-9. You may be requested to sign by the withholding agent even if items 1, 3, and 5 below indicate otherwise.

For a joint account, only the person whose TIN is shown in Part I should sign (when required).

1. Interest, dividend, and barter exchange accounts opened before 1984 and broker accounts considered active during 1983. You must give your correct TIN, but you do not have to sign the certification.

2. Interest, dividend, broker, and barter exchange accounts opened after 1983 and broker accounts considered inactive during 1983. You must sign the certification or backup withholding will apply. If you are subject to backup withholding and you are merely providing your correct TIN to the requester, you must cross out item 2 in the certification before signing the form.

3. Real estate transactions. You must sign the certification. You may cross out item 2 of the certification.

4. Other payments. You must give your correct TIN, but you do not have to sign the certification unless you have been notified that you have previously given an incorrect TIN. "Other payments" include payments made in the course of the requester's trade or business for rents, royalties, goods (other than bills for merchandise), medical and health care services (including payments to corporations), payments to a nonemployee for services, payments to certain fishing boat crew members and fishermen, and gross proceeds paid to attorneys (including payments to corporations).

5. Mortgage interest paid by you, acquisition or abandonment of secured property, cancellation of debt, qualified state tuition program payments, IRA or MSA contributions or distributions, and pension distributions. You must give your correct TIN, but you do not have to sign the certification.

Privacy Act Notice

Section 6109 of the Internal Revenue Code requires you to give your correct TIN to persons who must file information returns with the IRS to report interest, dividends, and certain other income paid to you, mortgage interest you paid, the acquisition or abandonment of secured property, cancellation of debt, or contributions you made to an IRA or MSA. The IRS uses the numbers for identification purposes and to help verify the accuracy of your tax return. The IRS may also provide this information to the Department of Justice for civil and criminal litigation, and to cities, states, and the District of Columbia to carry out their tax laws.

You must provide your TIN whether or not you are required to file a tax return. Payers must generally withhold 31% of taxable interest, dividend, and certain other payments to a payee who does not give a TIN to a payer. Certain penalties may also apply.

What Name and Number To Give the Requester

For this type of account:	Give name and SSN of:
1. Individual	The individual
2. Two or more individuals (joint account)	The actual owner of the account or, if combined funds, the first individual on the account [1]
3. Custodian account of a minor (Uniform Gift to Minors Act)	The minor [1]
4. a. The usual revocable savings trust (grantor is also trustee)	The grantor-trustee [1]
b. So-called trust account that is not a legal or valid trust under state law	The actual owner [1]
5. Sole proprietorship	The owner [3]
For this type of account:	**Give name and EIN of:**
6. Sole proprietorship	The owner [3]
7. A valid trust, estate, or pension trust	Legal entity [4]
8. Corporate	The corporation
9. Association, club, religious, charitable, educational, or other tax-exempt organization	The organization
10. Partnership	The partnership
11. A broker or registered nominee	The broker or nominee
12. Account with the Department of Agriculture in the name of a public entity (such as a state or local government, school district, or prison) that receives agricultural program payments	The public entity

[1] List first and circle the name of the person whose number you furnish. If only one person on a joint account has an SSN, that person's number must be furnished.

[2] Circle the minor's name and furnish the minor's SSN.

[3] You must show your individual name, but you may also enter your business or "DBA" name. You may use either your SSN or EIN (if you have one).

[4] List first and circle the name of the legal trust, estate, or pension trust. (Do not furnish the TIN of the personal representative or trustee unless the legal entity itself is not designated in the account title.)

Note: *If no name is circled when more than one name is listed, the number will be considered to be that of the first name listed.*

SPEAKER AVAILABILITY

The Role of Interferon alfa in Superficial Bladder Carcinoma
Advisory Board Meeting Series 2001

TO: Nancy Wilson, Projects In Knowledge
PH: 856-347-3121
FX: 860-347-6110

FROM: _____

DATE: _____

Below is a list of the proposed meeting cities and dates for the 4-hour advisory board meetings. Please indicate with an "X" your availability to participate as a speaker. This will assist us in moving forward with speaker and site confirmations. As the schedule and locations are finalized, I will contact you.

Saturday, November 17	Absecon, NJ	_____
	Aptos, CA	_____
Saturday, December 1	Ft. Lauderdale, FL	_____
	Farmington, PA	_____
Saturday, December 8	Marina del Rey, CA	_____
	San Antonio, TX	_____

FACULTY PLANNING MEETING
The Role of Interferon alfa in Superficial Bladder Carcinoma
Kenilworth, NJ ♦ September 28, 2001

Faculty Evaluation Form

Please complete the following faculty meeting evaluation form. Feel free to use the back of this form or another page for additional comments. You may fax the completed form to Projects In Knowledge at 201-617-5606, Attention: Beth Monica.

As an organization committed to excellence, Projects In Knowledge depends on your feedback to advance our continuous quality improvement goals on behalf of physicians participating in our activities. Our work with you to plan, implement, and evaluate our programming enables us to continue providing highest quality activities to physicians across the country.

I. Please rate the following elements:

	Strongly agree 5	4	3	2	Strongly disagree 1
Planning					
1. Schedule allowed adequate time for preparation.	❑	❑	❑	❑	❑
2. Project coordination was efficient.	❑	❑	❑	❑	❑
3. Communication with Projects In Knowledge was purposeful and effective.	❑	❑	❑	❑	❑
Content					
1. Topics discussed were relevant to participants' needs.	❑	❑	❑	❑	❑
2. The agenda allowed adequate opportunities for discussion and/or Q & A.	❑	❑	❑	❑	❑
3. This was an effective format for addressing the issues related to the topic.	❑	❑	❑	❑	❑
4. Supplementary written materials enhanced participants' learning.	❑	❑	❑	❑	❑
Logistics					
1. Onsite meeting staff was helpful.	❑	❑	❑	❑	❑
2. Facilities were adequate/appropriate.	❑	❑	❑	❑	❑
3. Faculty registration/onsite orientation was smooth and organized.	❑	❑	❑	❑	❑
4. Room arrangement facilitated instructional design.	❑	❑	❑	❑	❑

II. Please help us maintain high quality by completing the following section:

What do you consider were the greatest strengths/benefits of this meeting?	How might we improve this activity?
_____	_____
_____	_____
_____	_____

Please print name:_____

Job 1548—FACULTY PLANNING

FACULTY AFFILIATION/CONTACT FORM

Please return this form to Projects In Knowledge

The Role of Interferon alfa in Superficial Bladder Carcinoma

To: Beth Monica, Fax #: 201-617-5606

From: _____

RE: Faculty Affiliation/Contact Information

(INSTITUTIONAL INFORMATION (FOR INVITE/TITLE SLIDES/MEETING MATERIALS)

First Name:_____ Middle Initial:_____

Last Name:_____ Degree(s):_____

Title:_____

Institutional Affiliation:_____

_____

_____

_____

MAILING ADDRESS (FOR OVERNIGHT PACKAGES)

_____

_____

_____

_____

PHONE/FAX/E-MAIL/OFFICE CONTACT

Office Phone:_____ Office Fax:_____

E-mail Address: _____

Office Contact (assistant or secretary):_____

Office Contact Phone:_____

JOB #1548